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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/709,170	11/10/2000	Raymond P. Warrell	10412-025	4982

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EXAMINER
GIBBS, TERRA C

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 03/18/2003

16

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/709,170	Applicant(s) WARRELL ET AL.	
	Examiner Terra C. Gibbs	Art Unit 1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-23 and 29-33* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-23 and 29-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Response to Amendment

Applicant's Amendment filed 12/17/02, in Paper No. 15 is acknowledged. Claims 24-28 have been canceled.

Claims 1-23 and 29-33 are pending in the instant application.

Information Disclosure Statement

The information disclosure statement filed, November 10, 2000 has been placed in the application file, but the information referred to therein has not been considered. It is noted that applicant has indicated that all references were submitted, however, no references could be located in the application. Applicant is asked to resubmit all the references contained in the information disclosure statement so that they can be considered.

Nucleotide and/or Amino Acid Sequence Disclosure

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR §1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 §1.821 through 1.825 for the reason(s) set forth below. Applicant's attention is directed to these regulations, published at

1114 OG 29, May 15, 1990 and at 55 Fed. Reg. 18230, May 1, 1990. It is noted that the application fails to comply with 37 CFR §1.821(a) and (d).

37 CFR §1.821(d) states, "Where the description or claims of a patent application discuss a sequence that is set forth in the "Sequence Listing" in accordance with paragraph (c) of this section, reference must be made to the sequence by use of the sequence identifier, preceded by "SEQ ID NO:" in the text description or claims, even if the sequence is also embedded in the text of the description or claims of the patent application".

Applicant's Amendment, filed 3/29/02, in Paper No. 11, is not sufficient to bring the application into compliance with the sequence rules because the specification at 16, line 6 and page 31, line 4 contains the following sequence: 5'TCTCCCAGCGTGCGCCAT3'. A SEQ ID NO. does not follow this sequence. The above is an example and is not intended to indicate that the Examiner has made an exhaustive review of the application. Applicant must fully comply with the sequence rules for any response to this action to be considered fully responsive.

Priority

An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification or in an application data sheet (37 CFR 1.78(a)(2) and (a)(5)). For example, the first line of the instant specification should read, "This application claims the benefit of USSN 60,227,970, filed 8/25/00 and USSN 60,237,009, filed 9/29/00". Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 12, 19, 29 and 30 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 12, 19, 29 and 30 recite the term "reduced dose". The term "reduced dose" in claims 12, 19, 29 and 30 is a relative term which renders the claims indefinite. The term "reduced dose" is not defined by the claims and the specification does not provide a standard for ascertaining the requisite degree, and one of skill in the art would not be reasonably apprised of the metes and bounds of the invention. The specification at page 7, lines 11-19, defines, "reduced dose" as "a dose that is below the normally administered range, i.e. below the standard dose as suggested by the Physicians' Desk Reference, 54th Edition (2000) or a similar reference". However, the specification does not provide a standard for ascertaining a "reduced dose". Clarification is required.

Claim Rejections - 35 USC § 112

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

The 35 U.S.C. 112, first paragraph rejection against claims 1-23 has been withdrawn in view of Applicants arguments.

Claim Rejections - 35 USC § 102

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1-5 and 13-18, remain rejected under 35 U.S.C. 102(b) as being anticipated by Webb et al., (The Lancet, 1997 Vol. 349:1137-1141) for reasons of record set forth in the previous office action of 7/17/02.

Applicant's arguments filed 12/17/02 have been fully considered but they are not persuasive. Applicants in response to the previous office action, argue that Webb et al. discloses a treatment protocol wherein a bcl-2 antisense oligonucleotide is administered at dosages of 4.6 to 73.6 mg/m^2 for 14 days. Applicants further argue that Webb et al. do not describe treating or preventing caner in a human for a period less than 14 days. These arguments have been fully considered but are not persuasive.

Webb et al. disclose a daily subcutaneous infusion of a fully phosphorothioated bcl-2 antisense administered for 2 weeks to nine patients with non-Hodgkin's lymphoma (see page 1137, Methods). Webb et al. further disclose the daily dose of bcl-2 antisense was increased incrementally from 4.6 mg/m^2 to 73.6 mg/m^2 for 14 days (see page 1137, Findings). Webb et al. further evaluate the levels of bcl-2 measured by flow cytometry in lymph nodes of patient 6 during 7 and 14 days (see Figure 2). This evaluation by Webb et al. encompasses a period less than 14 days and thus anticipates claims 1-5, 13-18 and 24-28.

Therefore, Webb et al. anticipate the instant invention.

The 35 U.S.C. 102(b) rejection against claims 31-33 as being unpatentable over Webb et al. has been withdrawn in view of Applicants arguments.

The 35 U.S.C. 102(b) rejection against claims 1-5, 13-18, 24-28 and 31-33 as being unpatentable over Waters et al. (Journal of Clinical Oncology, 2000 Vol. 18:1812-1823) has been withdrawn in view of Applicants arguments.

The 35 U.S.C. 102(b) rejection against claims 1-5, 13-18, 24-28 and 31-33 as being unpatentable over Morris et al. (Proceedings of the American Society of Clinical Oncology, 1999 Vol. 18:323a) has been withdrawn in view of Applicants arguments.

The 35 U.S.C. 102(b) rejection against claims 1-6, 9-12, 13-19, 24, 26-29 and 31-33 as being unpatentable over Jansen et al. (Proceedings of the American Society of Clinical Oncology, 1999 Vol. 19:531a) has been withdrawn in view of Applicants arguments.

The 35 U.S.C. 102(b) rejection against claims as being unpatentable over Jansen et al., (The Lancet, 2000 Vol. 356:1728-33) has been withdrawn in view of Applicants arguments.

Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

The 35 U.S.C. 103(a) rejection against claims 1-33 in view of Raynaud et al., in further view of Lopes de Menezes et al., Miayake et al., Cotter et al., Webb et al. and Bennett et al. has been withdrawn in view of Applicants arguments.

Claims 1, 6-11 and 13-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Webb et al., (The Lancet, 1997 Vol. 349:1137-1141) in view of Jansen et al. (Proceedings of the American Society of Clinical Oncology, 1999 Vol. 19:531a).

Claim 1 is drawn to a method of treating or preventing cancer in a human comprising administering a bcl-2 antisense oligonucleotide at a dose of 0.01 to 50 mg/kg/day for a period consisting of 2 to 13 days. Claim 6 depends from claim 1 and further comprises administering one or more cancer therapeutics. Claims 9-11 depend from claim 6, and are directed to the embodiments of the method of claim 6, wherein the cancer therapeutic is administered concurrently with the bcl-2 antisense oligonucleotide; wherein the cancer therapeutic is a chemoagent, radiotherapeutic, immunotherapeutic, cancer vaccine, anti-angiogenic agent, cytokine, gene therapeutic, or hormonal agent; wherein the cancer therapeutic is a chemoagent, wherein the chemoagent is dacarbazine, docetaxel, paclitaxel, cisplatin, 5-fluorouracil, doxorubicin, etoposide, cyclophosphamide, fludarabine, irinotecan or cytosine arabinoside (Ara-C). Claims 7 and 8 depend from claim 6, and are directed to the embodiments of the method of claim 6, wherein the cancer therapeutic follows or precedes administration of the bcl-2 antisense.

Claims 13-18 depend from claim 6, and are drawn to a method of treating or preventing cancer in a human comprising administering a bcl-2 antisense oligonucleotide at a dose of 0.01 to 50 mg/kg/day for a period consisting of 2 to 13 days and further administering one or more cancer therapeutics; wherein said administration is by oral, intravenous infusion, subcutaneous injection, intramuscular injection, topical, depo injection, implantation, time-release mode, intracavitary, intranasal, inhalation, intratumor or intraocular administration; wherein said cancer is a cancer of the hematopoietic system, skin, bone and soft tissue, reproductive system, genitourinary system, breast, endocrine system, brain, central nervous system, peripheral nervous system, kidney, lung, respiratory system, thorax, gastrointestinal and alimentary canal, lymph nodes, pancreas, hepatobiliary system, or cancer of unknown primary site; wherein said cancer is non-Hodgkin's lymphoma, Hodgkin's lymphoma, leukemia, colon carcinoma, rectal carcinoma, pancreatic cancer, breast cancer, ovarian cancer, prostate cancer, renal cell carcinoma, hepatoma, bile duct carcinoma, choriocarcinoma, cervical cancer, testicular cancer, lung carcinoma, bladder carcinoma, melanoma, head and neck cancer or brain cancer, wherein the antisense oligonucleotide is from 10 to 35 bases and is complementary to the pre-mRNA or mRNA encoding the bcl-2 gene; wherein the antisense oligonucleotide comprises at least two phosphorothioate linkages; wherein the antisense oligonucleotide comprises the sequence of SEQ ID NO:17.

Webb et al. disclose a daily subcutaneous infusion of a fully phosphorothioated bcl-2 antisense, 18 base pairs in length, administered for 2 weeks to nine patients with non-Hodgkin's lymphoma (see page 1137, Methods). Webb et al. further disclose the daily dose of bcl-2 antisense was increased incrementally from 4.6 mg/m^2 to 73.6 mg/m^2 for 14 days (see page 1137,

Findings). Webb et al. further evaluate the levels of bcl-2 measured by flow cytometry in lymph nodes of patient 6 during 7 and 14 days (see Figure 2).

Webb et al. do not teach further administering one or more cancer therapeutics.

Jansen et al. teach the intravenous infusion of bcl-2 antisense, G3139, at doses of 0.6, 1.3, 1.7, and 2.3 mg/kg/day for 14 days, in combination with therapeutic agent, dacarbazine, in patients with advanced malignant melanoma (see Abstract). Jansen et al. further teach antisense oligonucleotide therapy combined with therapeutic agents, such as dacarbazine, are a novel and rational approach to improve response to chemotherapy (see Abstract).

It would have been *prima facie* obvious at the time the invention was made for one of ordinary skill in the art to devise a method of treating or preventing cancer in a human comprising administering a bcl-2 antisense oligonucleotide at a dose of 0.01 to 50 mg/kg/day for a period consisting of 2 to 13 days of Webb et al., and further administer one or more cancer therapeutics of Jansen et al. with a reasonable expectation of success. One of ordinary skill in the art would have been motivated to combine the bcl-2 antisense oligonucleotide regimen of Webb et al. with the cancer therapeutics of Jansen et al. because combined therapy of dacarbazine and bcl-2 antisense are a novel and rational approach to improve response to chemotherapy (see Jansen et al.). One of ordinary skill in the art would have been motivated to administer the cancer therapeutic following, preceding, or concurrent with the bcl-2 antisense oligonucleotide because these type of scheduled regimens were well known in the art at the time of the filing of the instant invention for optimizing maximal benefit and efficacy for therapeutic purposes.

Claims 1, 6, 10, 12, 19 and 29-33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Webb et al., and Jansen et al. as cited in the 35 U.S.C. 103(a) rejection against claims 6, 9, 10 and 11 in further view of Klasa et al. (Clinical Cancer Research, 2000 Vol. 6:2492-2500).

Claim 1 is drawn to a method of treating or preventing cancer in a human comprising administering a bcl-2 antisense oligonucleotide at a dose of 0.01 to 50 mg/kg/day for a period consisting of 2 to 13 days. Claim 6 depends from claim 1 and further comprises administering one or more cancer therapeutics. Claim 10 depends from Claim 6, wherein the cancer therapeutic is a chemoagent, radiotherapeutic, immunotherapeutic, cancer vaccine, anti-angiogenic agent, cytokine, gene therapeutic, or hormonal agent. Claim 12 depends from claim 6, and is drawn to a method of treating or preventing cancer in a human comprising administering a bcl-2 antisense oligonucleotide at a dose of 0.01 to 50 mg/kg/day for a period consisting of 2 to 13 days and further administering one or more cancer therapeutics, wherein the cancer therapeutic is administered at a reduced dose. Claim 19 is drawn to a method of treating or preventing cancer in a human comprising administering a bcl-2 antisense oligonucleotide at a dose of 0.01 to 50 mg/kg/day and further administering one or more cancer therapeutics; wherein the cancer therapeutic is administered at a reduced dose. Claims 29 and 30 are drawn to a pharmaceutical composition comprising a bcl-2 antisense oligonucleotide, at a dose of 0.01 to 50 mg/kg/day or a dose of 10 to 50 mg/kg/day, respectively; in combination with a reduced dose of a cancer therapeutic agent. Claims 31-33 depend from claims 29 or 30, and are directed to the embodiments of the methods of claims 29 and 30, including an antisense oligonucleotide from 10 to 35 bases, complementary to the pre-mRNA or mRNA encoding the bcl-2 gene, wherein the

antisense oligonucleotide comprises at least two phosphorothioate linkages; wherein the antisense oligonucleotide comprises the sequence of SEQ ID NO: 17.

The teachings of Webb et al. and Jensen et al. have been discussed on page 8, last paragraph and page 9, second paragraph.

Webb et al. and Jensen et al. do not teach to a method of treating or preventing cancer in a human comprising administering a bcl-2 antisense oligonucleotide at a dose of 0.01 to 50 mg/kg/day for a period consisting of 2 to 13 days and further comprises administering one or more cancer therapeutics, wherein the cancer therapeutic is administered at a reduced dose.

Klasa et al. teach eradication of human Non-Hodgkin's Lymphoma in SCID mice by bcl-2 antisense oligonucleotides combined with a low-dose of the cancer therapeutic, cyclophosphamide. Klasa et al. further teach that improved clinical outcomes could be achieved with standard, or even lower doses of anticancer drugs when combined with antisense oligonucleotides, thus impacting overall clinical tolerance and costs of care (see page 2499, last paragraph).

It would have been *prima facie* obvious at the time the invention was made for one of ordinary skill in the art to devise a method of treating or preventing cancer in a human comprising administering a bcl-2 antisense oligonucleotide at a dose of 0.01 to 50 mg/kg/day for a period consisting of 2 to 13 days of Webb et al., and further administer one or more cancer therapeutics of Jansen et al. at a reduced dose as taught by Klasa et al. with a reasonable expectation of success. One of ordinary skill in the art would have been motivated to combine the bcl-2 antisense oligonucleotide regimen of Webb et al. with the cancer therapeutics of Jansen et al. at a reduced dose because clinical outcomes involving lower doses of anticancer drugs

when combined with antisense oligonucleotides results in improved clinical outcomes (see Klasa et al.).

Claims 19 and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Webb et al., Jansen et al. and Klasa et al. as cited in the 35 U.S.C. 103(a) rejection against claims 12, 19 and 29-33 in further view of Tortora et al. (Antisense and Nucleic Acid Drug Development, 1998 Vol. 8:141-145.

Claims 19 and 20 are drawn to a method of treating or preventing cancer in a human comprising administering a bcl-2 antisense oligonucleotide at a dose of 0.01 to 50 mg/kg/day and further administering one or more cancer therapeutics at a reduced dose; wherein the cancer therapeutic is paclitaxel and the dose is 10 to 135 mg/m^2/cycle.

The teachings of Webb et al. and Jensen et al. have been discussed on page 8, last paragraph and page 9, second paragraph. The teachings of Klasa et al. have been discussed on page 11, third paragraph.

Webb et al., Jensen et al. and Klasa et al. have not taught the cancer therapeutic is paclitaxel and the dose is 10 to 135 mg/m^2/cycle.

Tortora et al. teach the cooperative antitumor effect of mixed backbone oligonucleotides targeting protein kinase A in combination with cytotoxic drugs or biologic agents (see Abstract). Tortora et al. further teach that a mixed backbone oligonucleotide administered in a sequential schedule with paclitaxel, at a dose of 20 mg/kg, inhibited tumor and increased mice survival (see Figure 4).

It would have been *prima facie* obvious at the time the invention was made for one of ordinary skill in the art to devise a method of treating or preventing cancer in a human comprising administering a bcl-2 antisense oligonucleotide at a dose of 0.01 to 50 mg/kg/day for a period consisting of 2 to 13 days of Webb et al., and further administer one or more cancer therapeutics of Jansen et al. at a reduced dose as taught by Klasa et al. with a reasonable expectation of success. One of ordinary skill in the art would have been motivated to combine the bcl-2 antisense oligonucleotide regimen of Webb et al. with the cancer therapeutics of Jansen et al. at a reduced dose because clinical outcomes involving lower doses of anticancer drugs when combined with antisense oligonucleotides results in improved clinical outcomes (see Klasa et al.). One of ordinary skill in the art would have been motivated to administer paclitaxel at a dose of 10 to 135 mg/m^2/cycle since, at the time the invention was filed, it was well known in the art to range the dose to meet the maximal therapeutic benefit for a range of individuals.

Claims 19 and 21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Webb et al., Jansen et al. and Klasa et al. as cited in the 35 U.S.C. 103(a) rejection against claims 12, 19 and 29-33 in further view of Adjei et al. (Seminars in Oncology, 1999 Vol. 26:32-40).

Claims 19 and 21 are drawn to a method of treating or preventing cancer in a human comprising administering a bcl-2 antisense oligonucleotide at a dose of 0.01 to 50 mg/kg/day and further administering one or more cancer therapeutics at a reduced dose; wherein the cancer therapeutic is docetaxel and the dose is 6 to 60 mg/m^2/cycle.

The teachings of Webb et al. and Jensen et al. have been discussed on page 8, last paragraph and page 9, second paragraph. The teachings of Klasa et al. have been discussed on page 11, third paragraph.

Webb et al., Jensen et al. and Klasa et al. have not taught the cancer is docetaxel and the dose is 6 to 60 mg/m^2/cycle.

Adjei et al. teach docetaxel and irinotecan, alone and in combination, in the treatment of non-small cell lung cancer (see Abstract). Adjei et al. further teach docetaxel is typically administered in doses ranging from 60 to 100 mg/m^2 (see page 34, first column).

It would have been *prima facie* obvious at the time the invention was made for one of ordinary skill in the art to devise a method of treating or preventing cancer in a human comprising administering a bcl-2 antisense oligonucleotide at a dose of 0.01 to 50 mg/kg/day for a period consisting of 2 to 13 days of Webb et al., and further administer one or more cancer therapeutics of Jansen et al. at a reduced dose as taught by Klasa et al. with a reasonable expectation of success. One of ordinary skill in the art would have been motivated to combine the bcl-2 antisense oligonucleotide regimen of Webb et al. with the cancer therapeutics of Jansen et al. at a reduced dose because clinical outcomes involving lower doses of anticancer drugs when combined with antisense oligonucleotides results in improved clinical outcomes (see Klasa et al.). One of ordinary skill in the art would have been motivated to administer docetaxel at a dose of 6 to 60 mg/m^2/cycle since, at the time the invention was filed, it was well known in the art to range the dose to meet the maximal therapeutic benefit for a range of individuals.

Claims 19 and 22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Webb et al., Jansen et al. and Klasa et al. as cited in the 35 U.S.C. 103(a) rejection against claims 12, 19 and 29-33 in further view Foran et al. (Journal of Clinical Oncology, 1999 Vol. 17:546-53).

Claims 19 and 22 are drawn to a method of treating or preventing cancer in a human comprising administering a bcl-2 antisense oligonucleotide at a dose of 0.01 to 50 mg/kg/day and further administering one or more cancer therapeutics at a reduced dose; wherein the cancer therapeutic is fludarabine and the dose is 2.5 to 25 mg/m^2/cycle.

The teachings of Webb et al. and Jensen et al. have been discussed on page 8, last paragraph and page 9, second paragraph. The teachings of Klasa et al. have been discussed on page 11, third paragraph.

Webb et al., Jensen et al. and Klasa et al. have not taught the cancer therapeutic is fludarabine and the dose is 2.5 to 25 mg/m^2/cycle.

Foran et al. teach a multicenter phase II study of fludarabine phosphate for patients with newly diagnosed lymphoplasmacytoid lymphoma (see Abstract). Foran et al. further teach seventy eight patients were administered fludarabin, at a dose of 25 mg/m^2 in 5-day cycles, every 4 weeks. Foran et al. further teach this regimen induces remission in more than half of the treated patients (see Figure 1).

It would have been *prima facie* obvious at the time the invention was made for one of ordinary skill in the art to devise a method of treating or preventing cancer in a human comprising administering a bcl-2 antisense oligonucleotide at a dose of 0.01 to 50 mg/kg/day for a period consisting of 2 to 13 days of Webb et al., and further administer one or more cancer therapeutics of Jansen et al. at a reduced dose as taught by Klasa et al. with a reasonable

expectation of success. One of ordinary skill in the art would have been motivated to combine the bcl-2 antisense oligonucleotide regimen of Webb et al. with the cancer therapeutics of Jansen et al. at a reduced dose because clinical outcomes involving lower doses of anticancer drugs when combined with antisense oligonucleotides results in improved clinical outcomes (see Klasa et al.). One of ordinary skill in the art would have been motivated to administer fludarabine at a dose of 2.5 to 25 mg/m^2/cycle since, at the time the invention was filed, it was well known in the art to range the dose to meet the maximal therapeutic benefit for a range of individuals.

Claims 19 and 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Webb et al., Jansen et al. and Klasa et al. as cited in the 35 U.S.C. 103(a) rejection against claims 12, 19 and 29-33 in further view Murren et al. (Caner Chemotherapy Pharmacology, 2000 Vol. 46:43-50).

Claims 19 and 23 are drawn to a method of treating or preventing cancer in a human comprising administering a bcl-2 antisense oligonucleotide at a dose of 0.01 to 50 mg/kg/day and further administering one or more cancer therapeutics at a reduced dose; wherein the cancer therapeutic is irinotecan and the dose is 5 to 50 mg/m^2/cycle.

The teachings of Webb et al. and Jensen et al. have been discussed on page 8, last paragraph and page 9, second paragraph. The teachings of Klasa et al. have been discussed on page 11, third paragraph.

Webb et al., Jensen et al. and Klasa et al. have not taught the cancer therapeutic is irinotecan and the dose is 5 to 50 mg/m^2/cycle.

Murren et al. teach the dose escalation and pharmacokinetic study of irinotecan in combination with paclitaxel in patients with advanced cancer (see Abstract). Murren et al. further teach irinotecan was given as a 90-minute infusion at a starting dose of 50 mg/m^2 (see page 44, second column). Murren et al. further teach a starting dose of 50 mg/m^2 is in agreement with other reported values for irinotecan given alone (see page 48, second column).

It would have been *prima facie* obvious at the time the invention was made for one of ordinary skill in the art to devise a method of treating or preventing cancer in a human comprising administering a bcl-2 antisense oligonucleotide at a dose of 0.01 to 50 mg/kg/day for a period consisting of 2 to 13 days of Webb et al., and further administer one or more cancer therapeutics of Jansen et al. at a reduced dose as taught by Klasa et al. with a reasonable expectation of success. One of ordinary skill in the art would have been motivated to combine the bcl-2 antisense oligonucleotide regimen of Webb et al. with the cancer therapeutics of Jansen et al. at a reduced dose because clinical outcomes involving lower doses of anticancer drugs when combined with antisense oligonucleotides results in improved clinical outcomes (see Klasa et al.). One of ordinary skill in the art would have been motivated to administer irinotecan at a dose of 5 to 50 mg/m^2/cycle since, at the time the invention was filed, it was well known in the art to range the dose to meet the maximal therapeutic benefit for a range of individuals.

Conclusion

No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Terra C. Gibbs whose telephone number is (703) 306-3221. The examiner can normally be reached on M-F 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on (703) 308-0447. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 746-8693 for regular communications and (703) 872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

tcg
March 6, 2003

RAM R. SHUKLA, PH.D
PATENT EXAMINER